

Psychomotor Development of Children from an Iodine-Deficient Region

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Objectives To assess the psychomotor development of the progeny of women from a moderately iodine-deficient area for whom thyroid function during pregnancy was measured.

Study design The development of 86 children was assessed by the Bayley Scale of Infant Development at 12, 18, and 24 months.

Results Maternal serum free thyroxine (FT₄) levels in the first trimester of pregnancy were the major determinant of psychomotor development at 18 and 24 months. Children born from mothers with FT₄ levels <25th percentile (<10 pg/mL) had an OR of 2.1 for mild-to-severe delay. Furthermore, alterations in behavior were already observed at 12 months and were related to subsequent changes in development. Neonatal thyroid status did not influence development.

Conclusions This study highlights the need to implement active measures of iodine supplementation periconceptionally and during pregnancy and lactation because the negative effects on development and behavior might be prevented through preemptive action. (*J Pediatr* 2011; ■: ■-■).

Adequate amounts of thyroid hormones are critical for nervous system function throughout life, but particularly during development. Thyroid hormones regulate cerebral cytoarchitecture, neuronal growth, and synaptogenesis, and their receptors are widely distributed in the central nervous system.¹⁻⁵ The fetus relies on the mother for the supply of thyroid hormones because its thyroid only secretes significant amounts of thyroxine (T₄) after midgestation. Accordingly, maternal hypothyroxinemia, regardless of the cause, leads to decreased availability of T₄ for the fetal brain and has been described to impair neuropsychological development in the progeny.⁶

Iodine is required for thyroid hormone synthesis, and an adequate iodine intake is necessary for thyroid hormone homeostasis. The World Health Organization states that iodine deficiency (ID), the major cause of maternal hypothyroxinemia (regardless of whether the mother has normal thyroid function), is the greatest contributing factor, after starvation, to mental retardation in children. The most serious consequence of ID is neurologic cretinism in areas of severe deficiency (urinary iodine [UI] excretion <25 µg/L), but, of note, children's development is still affected in areas of mild to moderate deficiency (UI excretion 25 to 100 µg/L).⁷

Normal infant development is a global process by which the child acquires complex skills and knowledge. Development is a continuous, dynamic, and irreversible progression that encompasses three main development domains: cognitive, motor, and psychosocial. Satisfactory cognitive and motor development requires a well-formed and normally functioning nervous system, as well as an environment that provides adequate nutrition, opportunities to learn and practice, challenges and rewards.⁸ Furthermore, it is recognized that, altogether, genetics, in utero environment, and individual intrinsic postnatal factors cannot be dissociated from the child's immediate (family) and broader social (community, political, and social structure) environment, and that the impact of this interaction has repercussions throughout life.^{9,10}

Maternal hypothyroidism^{11,12} and hypothyroxinemia¹²⁻¹⁶ are related to adverse psychomotor development. Hypothyroxinemia is also linked to attention deficit, hyperactivity disorders¹⁷ and autism, influencing mood and behavior.¹⁸ More specifically, studies from ID areas show a correlation between maternal serum T₄ levels and subsequent motor and cognitive function in children¹⁹ and between mothers with hypothyroxinemia and impaired intellectual and motor function of progeny.²⁰

FT ₃	Free triiodothyronine
FT ₄	Free thyroxine
ID	Iodine deficiency
MDI	Mental Development Index
PDI	Psychomotor Development Index
T ₄	Thyroxine
TT ₃	Total triiodothyronine
TT ₄	Total thyroxine
TSH	Thyroid stimulating hormone
UI	Urinary iodine

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Although there is clear evidence that thyroid impairment, whatever its cause, compromises development of the central nervous system, studies are still lacking on the identification of a marker(s) that may predict deleterious consequences for the child throughout development. We performed a longitudinal study to assess correlations of maternal thyroid function in the three trimesters of pregnancy, with that of the child's in the neonatal period, and the child's cognitive, motor, and behavioral development to 2 years of age, in the context of iodine deficiency.

Methods

The study was carried out at the Centro Hospitalar do Alto Ave, EPE-Guimarães, Portugal. Between January of 2003 and December of 2005, 140 pregnant women, consecutively entering the antenatal clinic, were invited to assess thyroid function during and after pregnancy. The exclusion criteria comprised use of drugs or iodinated antiseptics, pregnancy with multiple fetuses, history of previous diabetes, infertility treatment, malformation of the fetus, known thyroidal and other endocrine dysfunctions, and heavy smoking (more than 10 cigarettes/d). One pregnancy terminated with a fetal loss, six pregnancies were of multiple fetuses, one newborn died in the neonatal intensive care unit, and no data were available for one child. Of 131 children born, those with risk factors for delayed outcome (severe neonatal disease, chronic condition, long-term medication, severe disability, gestational age less than 34 weeks, birth weight less than 2000 g, single-parent family) were excluded, as well as those who had fewer than two psychomotor development evaluations. Eighty-six children remained for the complete study. Newborns were evaluated on day 3 after birth in the context of the national screening for congenital hypothyroidism and in the outpatient clinic at 12, 18, and 24 months of age. The study design and procedures were approved by the hospital's research ethical committee. All women gave informed written consent for their enrollment and that of their offspring. Demographic and clinical information of the mothers and progeny was obtained and adjusted for potential confounding effects: maternal age, parity, socioeconomic-cultural status, length of breast feeding, use of alcohol and tobacco during pregnancy, children's sex, gestational age, type of delivery, Apgar's score, birth weight, body length, and head circumference. The social, economic, and cultural status was assessed by the Graffar scale, which includes information on the type of employment and education of the women and their partners, family income, characteristics of the house and type of neighborhood.²¹

Assessment of Iodine Status and Thyroid Function

The following tests were performed on the serum of neonates: total thyroxine (TT₄), free T₄ (FT₄), and total triiodothyronine (TT₃) using of the DYNOtest radioimmunoassay reagents (Brahms Diagnostica GmbH, Berlin, Germany).

When there was insufficient serum to determine all thyroid hormone test results, the order of choice for the analysis was TT₄, FT₄, and TT₃. Maternal thyroid hormones and urinary iodine concentrations in the three trimesters of pregnancy and until 1 year after delivery, including offspring thyroid-stimulating hormone (TSH) and urinary iodine levels in the neonatal period, were reported previously.^{22,23} Because FT₄ kits used for diagnosis do not account for changes in the concentration of thyroid hormone carrier proteins, such as is the case during pregnancy (because of the increase in the concentration of thyroxine-binding globulin), and because we were searching for a predictive marker, we further evaluated FT₄ in the first trimester of pregnancy by use of two additional measurement methods in a selected number of first-trimester samples (systematic sampling of still available samples) by use of two other independent tests: the Immunotech FT₄ radioimmunosorbent assay kit (Beckman Coulter, Prague, Czech Republic) that uses the same methodological principle as the one by Brahms; and by equilibrium dialysis with the Direct Free T₄ by Dialysis kit (IVD Technologies, Santa Ana, California).

Assessment of Infant's Development

Infant's development was assessed by the Bayley Scale of Infant Development, version I²⁴ at 12, 18, and 24 months. This instrument is intended to measure a child's level of development in the cognitive, motor and behavior domains. The Bayley Scale of Infant Development evaluation is performed by presenting a series of test materials to the child and scoring responses by age to convert into the Mental Development Index (MDI) and the Psychomotor Development Index (PDI). The normal average score is of 100, with a SD of 16. A group difference between 0.5 to 1 SD (8 to 16 index points) is considered clinically relevant. Infants are classified as significantly delayed when MDI or PDI is <68 (>2 SD under the mean); mildly delayed when having an index between 68 and 83 (1 to 2 SD under the mean); within normal limits between 84 and 116 and accelerated when >116. Behavior is evaluated by the Infant Behavior Record, a scale that provides supplementary information gained from the mental and motor scales.²⁴

Statistical Analyses

Data are presented as mean \pm SD. Comparisons were made by use of the *t* test or the nonparametric Mann-Whitney test. Correlations between neonatal and maternal variables were performed with the Pearson correlation or Spearman rank correlation tests. ANOVA was used to compare several groups. Multiple comparisons were studied through the Tukey test. Receiver operator characteristic analysis was used to define thyroid hormones cutoff points. Linear regression models were studied for the relation of behavior variables and development. Values were considered significant when *P* < .05. All tests were two-sided. Statistical analyses were performed with the SPSS 17 software package (SPSS Inc, Chicago, Illinois). The Bland-Altman method²⁵ was used to

Table I. Results of infant mental and psychomotor development assessments at the ages of 12, 18, and 24 months

	MDI			PDI		
	12 mo (n = 79)	18 mo (n = 74)	24 mo (n = 86)	12 mo (n = 79)	18 mo (n = 74)	24 mo (n = 86)
Score (mean \pm SD)	97.2 \pm 17.5	98.2 \pm 15.0	100.2 \pm 18.2	93.7 \pm 11.4	96.4 \pm 12.9	95.7 \pm 11.3
Accelerated (no.)	10	3	15	1	5	2
Within normal limits (no.)	56	57	55	62	61	73
Mildly delayed (no.)	9	11	12	14	6	11
Significantly delayed (no.)	4	3	4	2	2	0
Mildly and significantly delayed (%)	16.5	18.9	18.6	20.3	10.8	12.8

determine whether the FT₄ values obtained from the three different measurement methods were comparable.

Results

Children's Characterization

Enrolled infants (n = 86) comprised 40 girls and 46 boys, born by vaginal delivery in 60% of the cases, with mean gestational age of 38.2 weeks (SD = 1.6), mean birth weight of 3187 g (SD = 440), mean birth length of 48.8 cm (SD = 2.1), and mean cephalic perimeter of 34.6 cm (SD = 1.4). All neonates had an Apgar score at the first minute \geq 6 and at the fifth minute \geq 8. None had abnormal results on the national screening program for congenital hypothyroidism. Newborn percentile for thyroid parameters were for TT₄ (ug/dL) (n = 80), 10th percentile: 12.0; 50th percentile: 17.7; and 90th percentile: 21.5; for FT₄ (pg/mL) (n = 79), 10th percentile: 13.7; 50th percentile: 18.9; and 90th percentile: 22.8; and for TT₃ (nmol/L) (n = 60), 10th percentile: 1.8; 50th percentile: 2.2; and 90th percentile: 3.0. Eight children (9.3%) were born before 37 weeks gestational age, and eight had low birth weight (<2500 g).

Mother's Characterization

The mothers, part of a larger population for whom detailed characterization of thyroid function has been previously described,^{22,23} had a mean age of 30.8 years old (SD = 6.5), one-half with a medium-high socioeconomic status and 2.5 average pregnancies (SD = 1.6). Eight women had antithyroidal antibodies with serum thyroid hormones levels (including FT₄), similar to those women without measurable antibodies. In the first trimester of pregnancy, 10th percentile for FT₄ was of 9.0 pg/mL and for 50th to 90th percentile was 11.1 to 13.7 pg/mL; five women had both FT₄ levels <10th percentile and UI <50 μ g/L. Two cases had FT₄ <10th percentile in the first and third trimesters. Women of higher socioeconomic class and less parity had higher UI values. There were no differences in women regarding age, previous pregnancies, and socioeconomic status related to FT₄ levels. The subset of the initial sample, for which confirmatory testing was performed, (91/146 for the Beckman Coulter kit and 70/146 for the equilibrium dialysis kit), showed good agreement with a 95% CI with the Bland-Altman method of comparison.²⁵ Therefore, for monitoring purposes, the data

suggest that the different measurement approaches used were appropriate and concordant.

Children's characteristics such as sex, gestational age, type of delivery, Apgar score, birth, body length, and cephalic perimeter at birth and length of breastfeeding were not statistically different comparing mothers with FT₄ levels <10th percentile (n = 8) to 50th to 90th percentile (n = 36) in the first trimester. For the same measurements no differences were noted between mothers with UI <50 μ g/L (n = 36) compared with mothers with >50 μ g/L (n = 47).

Developmental Assessment

Global results of psychomotor evaluations are shown in **Table I**. Of note, more than 10% of children displayed mild-to-significant delay at all assessment times (12, 18, and 24 months). Mental development index correlated negatively with the socioeconomic status at 18 and 24 months (Pearson coefficient of correlation of -0.67 and -0.88, respectively). No correlations were found between psychomotor development and children's sex, Apgar score, gestational age (only term babies were considered) and birth weight (only babies with birth weight >2500 g were considered), or mother's age, presence of antithyroidal antibodies, or previous pregnancies. Infants born by eutocic deliveries tended to perform better, however, without statistical significance.

Relationship between Mother's Thyroid Status and Infant Development

The relationship between maternal iodine and thyroid status, at different times of pregnancy, was assessed for mothers with altered thyroid function (cases) compared with those within normal limits (control subjects), on the progeny's psychomotor development. Serum thyroid level parameters were defined as TT₄, FT₄, TT₃, and FT₃, cases with levels <10th percentile and control subjects 50th to 90th percentile; TSH, cases with levels >90th percentile and control subjects 10th to 50th percentile; UI, cases with levels <50 μ g/L and control subjects \geq 50 μ g/L.

Table II lists the comparisons of the progeny's development at the different ages and thyroid function by trimesters; only those differences statistically significant (and clinically relevant) and nonstatistically significant but clinically relevant (group differences between 0.5 to 1 SD)

Table II. Relation between maternal iodine and thyroid status, for mothers with altered thyroid function (cases) compared with those within normal limits (controls), on the progeny's psychomotor development

Effect	Score (mean \pm SD)		Mother		
	Cases	Control subjects	Analyte	Trimester	Cases (control subjects)
MDI					
12 mo	90.7 \pm 14.5	102.6 \pm 18.1	TT ₃	3rd	7 (25)
	77.7 \pm 17.9*	99.3 \pm 17.6	FT ₃	3rd	9 (33)
	89.4 \pm 19.5	98.3 \pm 14.8	FT ₄	3rd	7 (25)
18 mo	88.9 \pm 12.8*	99.9 \pm 20.8	UI	3rd	23 (42)
	84.2 \pm 35.8	96.8 \pm 16.4	TT ₄	3rd	6 (23)
24 mo	93.8 \pm 16.3*	104.7 \pm 18.2	UI	1st	36 (47)
	94.2 \pm 15.1*	103.5 \pm 20.7	UI	3rd	26 (47)
	92.6 \pm 19.4	103.4 \pm 19.0	FT ₄	1st	8 (36)
	91.1 \pm 21.4	100.7 \pm 17.2	FT ₃	3rd	9 (33)
PDI					
18 mo	92.4 \pm 13.4*	99.1 \pm 12.3	UI	1st	28 (44)
	92.1 \pm 13.8*	98.7 \pm 12.0	UI	3rd	23 (42)
	85.9 \pm 20.0*	98.7 \pm 12.5	FT ₄	1st	7 (28)
	86.0 \pm 31.2	97.0 \pm 14.4	TT ₃	2nd	3 (29)
24 mo	84.4 \pm 10.9*	98.0 \pm 9.5	FT ₄	1st	8 (36)
	87.2 \pm 14.5	97.2 \pm 12.0	TT ₃	2nd	5 (34)

All MDI and PDI scores shown are clinically relevant.

*($P < .05$).

are shown. Serum values of TSH did not correlate to the children's development at any time during pregnancy. TT₄ and TT₃ were not statistically significantly different but displayed a trend for children's development; FT₄, FT₃, and iodine related significantly to psychomotor development. Women with levels of FT₄ <10th percentile had hypothyroxinemia or normal thyroid function. The mothers of the 15 children with accelerated mental performance by 24 months, compared with mothers of children with lower MDI, had lower FT₃ levels in the first trimester (mean \pm SD: 3.9 \pm 0.5 pg/mL vs 4.4 \pm 0.6 pg/mL, $P < .01$), and none had FT₄ levels <10th percentile.

Receiver operator characteristic analysis was performed to determine a cutoff value of maternal FT₄ that could be predictive of having a child with abnormal psychomotor development. Mothers with first-trimester FT₄ levels <10 pg/mL (approximately 25% of our sample) had an OR of 2.1 for having a child mildly or significantly delayed (with a PDI at 24 months <84, which is <1 SD below the mean).

The correlation between neonatal thyroid status and children's development also was assessed. Significant (although weak) correlations were found between neonatal serum levels of TT₃ and MDI 12 months (Pearson coefficient = -0.46), serum TSH and MDI 18 months (Pearson coefficient = -0.27) and FT₃ levels and PDI 24 months (Pearson coefficient = -0.52).

Effect of Maternal First-Trimester UI and FT₄ Levels on Infant's Behavior

The relation of maternal UI (Table III) and FT₄ levels in the first trimester with infant's behavior was assessed by BRI.

Children born from hypothyroxinemic euthyroid mothers showed less endurance at 12 months (less able to remain responsive to the demands of the tests; non-parametric comparisons, cases' mean rank = 13, control subjects' mean rank = 22, $P < .05$), and were fearless of strange situations by the age of 18 months (cases' mean rank = 10, controls' mean rank = 19, $P < .05$). Children born from iodine-deficient mothers performed with less endurance and attention and had lower persistence in a goal-direct effort, exhibiting a higher level of activity and reactivity (Table III).

Relation between Behavior, MDI, and PDI

At all assessment points (12, 18, and 24 months) the three motivation variables of behavior (endurance, intentionality, and attention span) correlated positively with each other, as well as with the MDI. The level of activity correlated negatively with endurance, intentionality, and attention span, having a negative impact on MDI (Table IV). Moreover, endurance, intentionality, and attention span at 12 months correlated with MDI and PDI at 18 months (data not shown). To establish a causal link between behavior items and MDI at 24 months, regression models were performed. Fifty percent of the observed variability on mental development at 24 months was explained by endurance at 18 months ($P = .023$) and intentionality ($P = .004$) and endurance at 24 months ($P = .032$) as explanatory variables.

Discussion

Our study is the most complete longitudinal assessment to date of the importance of maternal thyroid hormone and

Table III. Differences in children's behavior scale according to mothers' urinary iodine concentration in the first trimester of pregnancy

Characteristic	Mean rank	
	Cases (UI <50 µg/L)	Control subjects (UI ≥50 µg/L)
12 mo		
Fearfulness	32 (n = 36)	44 (n = 39)
Attention span	33 (n = 36)	44 (n = 40)
18 mo		
Fearfulness	25 (n = 27)	41 (n = 41)
Looking around	41 (n = 27)	32 (n = 41)
Manipulation (banging toys/hands)	28 (n = 27)	39 (n = 41)
Attention span	29 (n = 28)	41 (n = 43)
Intentionality (persistence in a goal-directed effort)	30 (n = 28)	40 (n = 43)
Endurance (ability to remain responsive to the demands of the test)	30 (n = 28)	40 (n = 43)
Level of energy	42 (n = 28)	32 (n = 43)
24 mo		
Intentionality	33 (n = 35)	48 (n = 47)
Reactivity (sensitivity or excitability to the environment or arousal)	47 (n = 35)	37 (n = 47)

Nonparametric comparisons. All values (cases) significant at $P < .05$.

iodine status during pregnancy on infant/child neurodevelopment. Altogether, our study demonstrates the close relation of different areas of development: changes in behavior appear earlier and impact on later development. In contrast, the correlation found between neonatal thyroid status and development was weak and not consistent. Therefore the major impact of thyroid hormones seems to occur during fetal life, especially before the onset of fetal thyroid function. These observations highlight the need for monitoring thyroid function during early pregnancy, corroborating data from other studies.^{1,6}

The results obtained from maternal thyroid and iodine status show that the progeny's psychomotor development related to all thyroid analytes except serum TSH levels, probably because these women had normal thyroid function. However, it seems that maternal FT₄ in the first trimester of pregnancy is a major determinant of the offspring's development. Accordingly, the relationship between early maternal serum FT₄ levels and children's development have been highlighted in the literature.^{12-16,26,27} Altogether, these studies, including our findings, substantiate that the availability of maternal FT₄ to the developing fetal brain is of greater importance than that of TT₃, given that fetal brain TT₃ is almost entirely generated locally from fetal serum T₄. Considering that fetal thyroid function is substantial from 20 weeks of gestation, reaching appreciable amounts by the third trimester, and that thyroid hormone receptors are found in fetal brain after 10 weeks of gestation, it is thought that fetal TT₃ brain levels depend on FT₄ serum levels. In turn, FT₄ levels depend on the amount of maternal FT₄ that reaches the placental barrier.^{1,6} We found that maternal hypothyroxinemia (low levels of FT₄) is associated with an increased risk of progeny's psychomotor delay (OR of 2.1) and a cutoff of FT₄ could be established to predict that risk. This was independent of the cause of hypothyroxinemia, supporting the hypothesis that any condition leading to maternal hypothyroxinemia can im-

pact the progeny's development.¹ We found no differences in thyroid hormone levels according to the presence of thyroid antibodies.

The finding that maternal serum FT₄ levels after midgestation seem not to be related with development outcome does not mean that the fetal brain no longer requires maternal thyroid hormones after the earlier phases of development. Iodine crosses the placenta and is critical for building fetal thyroid stores and for fetal thyroid hormone synthesis. In our study, FT₄ levels in the third trimester had clinically relevant impact on MDI at 12 months and iodine in the last trimester also was associated with differences in MDI/PDI at 18 months and with MDI at 24 months.

The progeny of mothers with hypothyroxinemia or iodine deficiency had a common developmental phenotype: decreased PDI by 18 months that at 24 months persisted and presented with mental impairment. However, by 12 months, while presenting a "normal" psychomotor development, as classified by the developmental indexes MDI and PDI, within a range of 100 ± 16 , these children exhibited lower levels of endurance and a shorter attention span, which seemed associated with some disruption in normal development in later ages. Specifically, mental development was related with intentional behavior (conduct toward a target) and attention. We found that the pattern of deficit of attention, perseverance, and intentionality, with a higher level of activity (especially after 18 months) correlated negatively with the mental index on later ages (data not shown). Furthermore, changes in endurance and intentionality accounted for 50% of the variability of mental development at 24 months. Although we cannot prove that attention deficit itself accounts for the variation in mental development at 24 months, as others described at 3 months,²⁸ endurance and intentionality are deeply linked to attention. In fact, endurance (understood as the ability to remain responsive to the demands of the test or the environment, or to persevere) and attention

Table IV. Correlations between behavior and mental development index at 12, 18, and 24 months

	Behavior				MDI	PDI
	Endurance	Attention	Intentionality	Level activity		
12 mo						
Endurance	—					
Attention	0.72	—				
Intentionality	0.71	0.76	—			
Level activity	NS	NS	NS	—		
MDI	0.38	0.27	0.33	NS	—	
PDI	NS	NS	NS	NS	0.46	—
18 mo						
Endurance	—					
Attention	0.50	—				
Intentionality	0.45	0.83	—			
Level activity	NS	−0.49	−0.39	—		
MDI	0.40	0.43	0.48	−0.25	—	
PDI	NS	NS	0.29	NS	0.54	—
24 mo						
Endurance	—					
Attention	0.57	—				
Intentionality	0.48	0.80	—			
Level activity	−0.23	−0.62	−0.49	—		
MDI	0.55	0.47	0.58	−0.37	—	
PDI	0.43	NS	NS	NS	0.49	—

All data shown expressed as Spearman correlation coefficient. Values significant at $P < .05$, except when noted nonsignificant (NS).

during the first year of life are described to correlate with mental tests, intelligence quotient, better performance in operative conditioning tests, academic performance, and learning skills.²⁹ The link between attention and thyroxine levels has been previously reported^{17,15,30} and may also underlie our observations.

Several limitations of the study should be noted, mainly the small size of the groups and the fact the mothers were selected from a hospital surveillance. Some bias also might have been introduced in the development assessment because the pediatrician who performed the development evaluation had access to the complete clinical history of the mother and child and also because assessing the development is in itself an early intervention. It also must be underlined that children's thyroid function was only studied at birth, and use of urinary iodine excretion to evaluate iodine status can only be done for epidemiologic purposes or cross-section studies. Nonetheless, while attending to the knowledge that the final outcome in development is influenced by many variables, we excluded most reported risks and protective factors related to development^{10,31} and solely included children with at least two assessments of development.

Although delayed motor performance found in our study seems to be a mild disability, this may influence the possibilities of the child to explore the environment and, consequently, impair development in general.³¹ In our cohort, one in four children had a relative risk of psychomotor development delay (both mild and significant) 2.1 times higher when related to maternal FT₄ levels <10 pg/mL in the first trimester of pregnancy. Even though obstetric associations worldwide have not reached consensus on universal study of thyroid function in pregnant women, it would seem wise to prescribe iodine supplements periconceptionally and during pregnancy and

lactation, because the negative effects on development and behavior might be prevented through preemptive action.^{7,27} ■

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